



TITLE:

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CITATION:

Tsujikawa, Akitaka ...[et al]. Treatment of polypoidal choroidal vasculopathy by intravitreal injection of bevacizumab.. Japanese journal of ophthalmology 2010, 54(4): 310-319

ISSUE DATE:

2010-07

URL:

<http://hdl.handle.net/2433/130712>

RIGHT:

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Title page

Title: Treatment of Polypoidal Choroidal Vasculopathy with Intravitreal Injection of Bevacizumab

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Running title: Bevacizumab for PCV

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The authors have no financial interest in the materials or devices mentioned in this
15 article.

Abstract

Purpose: To evaluate the efficacy of intravitreal bevacizumab (IVB) in eyes with polypoidal choroidal vasculopathy (PCV).

Methods: Seventeen eyes of 16 patients with subfoveal or juxtafoveal PCV were

5 treated with IVB. As an initial treatment, 10 eyes were treated with a single injection of bevacizumab and 7 eyes were treated with 3 monthly injections. Additional IVB injections were performed in 15 eyes when a recurrent or residual exudative change was seen. Follow-up after initiation of IVB ranged from 12 to 30 months (mean, 20.7 \pm 5.7 months).

10 **Results:** The mean foveal thickness before IVB (492 \pm 205 μ m) was decreased to 384 \pm 181 μ m at three months ($P = 0.0008$), and with additional IVB for recurrent exudative changes, the foveal thickness was still reduced significantly at 12 months (392 \pm 203 μ m, $P = 0.0270$). Mean visual acuity at baseline (0.54 \pm 0.38 in logMAR) somewhat improved to 0.45 \pm 0.32 at three months ($P = 0.156$). However, the

15 improvement in visual acuity then subsided, and returned to the pretreatment value at 12 months (0.54 \pm 0.39). **Conclusions:** In eyes with PCV, IVB can reduce the exudative change and can maintain visual function for at least one year.

Key words: age-related macular degeneration; bevacizumab; polypoidal choroidal vasculopathy

Introduction

It is generally thought that vascular endothelial growth factor (VEGF) plays a central role in the formation and development of choroidal neovascularization (CNV) in age-related macular degeneration (AMD).^{1,2} Visual prognosis in eyes with subfoveal CNV secondary to AMD is poor. Recently, a number of reports have shown promising effects of bevacizumab (Avastin; Genentech, South San Francisco, California), which is a recombinant humanized monoclonal antibody that binds to VEGF, for CNV secondary to AMD.³

Polypoidal choroidal vasculopathy (PCV) was first described as a new clinical entity with a unique form of choroidal vascular abnormality, which is characterized by a branching vascular network that terminates in polypoidal lesions seen on indocyanine green angiography.⁴⁻⁶ However, Maruko et al.⁷ recently reported that 5.5% of patients with exudative AMD showed PCV lesions in one eye and typical AMD lesions in the other eye. It is still controversial whether PCV is a distinct clinical entity or represents an unusual form of AMD.⁸ Similar to AMD,⁹ it has been reported that VEGF concentrations in aqueous humor are markedly increased in eyes with PCV.¹⁰ The involvement of VEGF in the formation of PCV is also suggested by histologic specimens.¹¹ Therefore, it may well be that anti-VEGF therapy is effective for the treatment of PCV.

Recently, several investigators have reported the effects of intravitreal bevacizumab (IVB) for the treatment of exudative PCV.¹²⁻¹⁹ Even though the polypoidal lesions sometimes persist after IVB injection, retinal thickness is reported to be decreased shortly after the initiation of such treatment.^{13-15, 17} In eyes with PCV, however, the effects of IVB on visual acuity (VA) remain controversial.^{13-15, 17} In addition, because these previous reports have only a short follow-up period, limited information is available on the long-term efficacy of IVB in eyes with PCV.¹³ Accordingly, the study described herein was designed to study for at least one year the effects of IVB administered for the treatment of PCV.

Material and Methods

For this interventional case series, we studied retrospectively the medical records of 17 eyes (16 patients) with active PCV that were treated with IVB at Kyoto University

Hospital from October 2006 to April 2008. All eyes had a minimum follow-up period

5 of 12 months after the initial treatment with IVB. The eligibility criteria were active

PCV with a visual disturbance and treatment with IVB. The diagnosis of PCV was

based on indocyanine green angiography, which shows a branching vascular network

that terminates in polypoidal swelling. In the current study, 15 eyes showed either a

polypoidal lesion, a branching vascular network, or type 2 CNV beneath the center of

10 the fovea. Two eyes showed a serous pigment epithelial detachment (PED) just

beneath the fovea with adjacent juxtafoveal polypoidal lesions. Eyes with other

macular abnormalities (i.e., AMD, pathologic myopia, idiopathic CNV, presumed

ocular histoplasmosis, angioid streaks and other secondary CNV) were excluded from

the current study. In the present study, pseudophakic eyes were included, but eyes

15 with a history of vitrectomy were excluded. Eyes that had undergone photodynamic

therapy (PDT) for PCV within four months were also excluded from the current study.

The current study was approved by the Institutional Review Board at Kyoto University

Graduate School of Medicine and adhered to the tenets of the Declaration of Helsinki.

Written informed consent was obtained from each patient.

In the study described herein, patients who had a subjective visual disturbance due to subfoveal or juxtafoveal PCV were offered IVB, the dosage of which was 1.25 mg/0.05 ml per injection. All injections were performed in a sterile manner and prophylactic topical antibiotics were applied for 1 week after IVB injection. As initial treatment, 10 eyes were treated with a single injection of bevacizumab and 7 eyes were treated with 3 monthly injections. Each patient was scheduled to visit our clinic for an examination at a 1-2 month interval. After the initial treatment, when recurrent or residual exudative changes due to PCV were seen by optical coherence tomography (OCT) examination or on a fundus examination, additional IVB injections were given.

At each visit, all patients underwent a comprehensive ophthalmologic examination, including best-corrected VA testing, intraocular pressure measurement, indirect ophthalmoscopy, slitlamp biomicroscopy with a contact lens, fundus photography, and OCT. Best-corrected VA was measured with a Landolt chart.

Fluorescein and indocyanine green angiography were performed on each patient using a confocal laser scanning system (HRA-2; Heidelberg Engineering, Heidelberg, Germany) before and at 3-6 months after the treatment. Additional angiography was performed as necessary.

In this study, spectral-domain OCT was used at the baseline examination and at

follow-up visits. At each visit, all patients underwent examination by OCT of cross-sections centered on the fovea as well as OCT of additional sections.

Because eyes with PCV often showed serosanguineous pigment epithelial detachment, foveal thickness was defined as the distance between the inner surface
5 of the neurosensory retina and the thin straight line of Bruch's membrane.¹⁴

All values are presented as mean \pm standard deviation. For statistical analysis, best-corrected VA measured with a Landolt chart was converted to a logarithm of the minimal angle of resolution (logMAR). Paired *t*-test was used to evaluate changes in VA and foveal thickness. In each eye, VA was considered to be improved or
10 deteriorated when the change in VA (logMAR) was greater than 0.3. Statistical software (Statview 5.0; SAS Institute, Cary, North Carolina) was used for statistical analyses. A *P* value < 0.05 was considered to be statistically significant.

RESULTS

In the current study, 17 eyes of 16 patients (14 men and 2 women), ranging in age from 60 to 85 years (74.8 ± 6.2 years), underwent IVB injection for the treatment of subfoveal or juxtafoveal PCV (Table 1). While 3 of 17 eyes had undergone PDT

5 previously, all eyes showed active exudative changes due to their PCV. No eyes had been treated previously with either local or systemic anti-VEGF therapy.

Examination just before initiation of the IVB treatment showed polypoidal lesions in 14 eyes, branching vascular network in all 17 eyes, type 2 CNV in 3 eyes, serous retinal detachment in 9 eyes, and PED in 10 eyes. Of the 17 eyes, subfoveal findings were

10 polypoidal lesions in 4 eyes, a branching vascular network in 11 eyes, and PED in 2 eyes. Pretreatment VA on a Landolt chart ranged from 0.09 to 1.2 (median, 0.3): five

of the 17 eyes had a VA of better than 0.5 (median, 0.8) before treatment. Fifteen

eyes received additional IVB injections. Mean total injections was 4.0 ± 1.7 , ranging

from 1 to 6. Follow-up after the initiation of IVB ranged from 12 to 30 months (mean,

15 20.7 ± 5.7 months).

Figure 1 shows the change in VA and in foveal thickness after IVB injection.

IVB treatment reduced substantially the exudative change after initiation of the treatment in 13 eyes (Fig. 2). The mean foveal thickness (492 ± 205 μ m before treatment) was decreased significantly to 384 ± 181 μ m ($P = 0.0008$) at three months.

After this successful initial treatment, however, six eyes showed a recurrence of the exudative change (Fig. 3). Repeated angiography confirmed a recurrence of polypoidal lesions in two eyes. With additional IVB, foveal thickness at 12 months (392 ± 203 μm) was still reduced significantly compared with pretreatment

5 measurements of thickness ($P = 0.0270$). The mean VA before treatment (0.54 ± 0.38 in logMAR) also somewhat improved, being 0.45 ± 0.32 ($P = 0.156$) at three months; the difference was not statistically significant. Unfortunately, the improvement in VA subsided thereafter. At 12 months, mean VA had returned to the pretreatment value (0.54 ± 0.39). At 12 months, two eyes showed a significant
10 improvement in VA and no eye showed a significant decrease in VA. Whether a single injection of IVB or 3 monthly IVB injections were given as the initial treatment, there was no significant difference in changes of either the VA or of the foveal thickness.

In the current study, 14 eyes showed polypoidal lesions just before treatment
15 with IVB, while postoperative angiography showed the polypoidal lesions to have disappeared in 9 eyes (Fig. 4). In no eye, however, had the branching vascular network disappeared. In addition, 3 eyes showed type 2 CNV just before the initiation of IVB. On postoperative angiography, leakage from the type 2 CNV had disappeared completely in 2 eyes and was substantially decreased in the other eye.

Figure 5 shows the change in VA and in foveal thickness after IVB in 5 eyes that had a good initial VA (better than 0.5 on a Landolt chart). The exudative change was reduced after the initiation of IVB treatment in all 5 of these eyes, and after this successful initial treatment, recurrent exudative change or macular edema was

5 treated with additional IVB injections. The mean VA (0.10 ± 0.11 in logMAR before treatment) was maintained at 12 months (0.13 ± 0.12) in all 5 eyes; one eye, however, developed a tear of the retinal pigment epithelium at 3 months after 3 monthly IVB injections (Fig. 6).

Discussion

PCV is thought to have a better visual prognosis than does AMD.²⁰ However, when the abnormal choroidal vasculature with exudative change extends to the subfoveal area, visual prognosis usually is poor. Direct laser photocoagulation has been applied to eyes with PCV.²¹ However, unless the entire lesion including the polypoidal lesion and a branching vascular network is successfully coagulated, the polypoidal lesion and exudative change often recur, resulting in decreased VA.²² A number of studies, however, have shown encouraging results of PDT for PCV.²³⁻²⁵ In a report by Chan et al.,²³ PDT resulted in stable or improved VA in 95% of eyes with PCV one year after treatment. However, recent studies have shown that visual prognosis of PCV treated with PDT is not so promising.²⁶⁻²⁸ One or more years after successful treatment with PDT, some eyes have a recurrence of PCV and, consequently, a decrease in VA.

Similar to AMD, some reports have suggested that VEGF is involved in the development of vascular lesions in eyes with PCV.^{10, 11} Recently, several investigators have reported the short-term effects of anti-VEGF therapy for the treatment of exudative PCV.^{12-19, 29} Originally, Ghajarnia et al.¹² reported a case of refractory PCV that was successfully treated with a single injection of IVB. Most subsequent reports have shown that IVB reduces the exudative change resulting from

PCV lesions shortly after the initiation of treatment, while exerting also an effect on the vascular lesions of PCV.^{13-15, 17} However, its effect on VA remains controversial.^{13-15,}

¹⁷ Gomi et al.¹⁴ reported no improvement in VA at three months after treatment of PCV with IVB. In contrast, Lai et al.¹³ and Song et al.¹⁵ reported a significant

5 improvement in VA at three months. However, because these reports each consisted of a small number of patients, selection of patients may have influenced the reported efficacy of treatment.^{13-15, 17} In addition, because each of these reports had a relatively short follow-up,^{14, 15, 17} the long-term effect of IVB on eyes with PCV is uncertain.

10 In the current study, follow-up after the initiation of IVB treatment was at least 12 months (mean, 20.7 ± 5.7 months). Similar to the previous reports, IVB treatment reduced substantially at three months the exudative change,^{13, 15, 17} and with additional IVB to recurrent exudative change, the decreased foveal thickness could be maintained for 12 months. With IVB, mean VA was also somewhat improved at three

15 months. This improvement in VA then subsided, and the mean VA returned to the pretreatment level at 12 months, even though the recurrent exudative change was often treated successfully with additional IVB. Judging from the current study, eyes with PCV that are treated with IVB can be expected to maintain the pretreatment VA for at least one year.

After the initial IVB treatment, our patients received additional IVB when a recurrent or persistent exudative change was seen. In both the MARINA³⁰ and ANCHOR³¹ studies, monthly treatments with ranibizumab successfully improved VA in eyes with AMD, while the PIER study³² showed that less frequent scheduled injections did not maintain the improvement in VA that was made with the initial monthly injections. However, it is still controversial whether additional treatment with ranibizumab to recurrent or persistent exudative change does maintain the improvement in VA that had been achieved with the initial treatment.³³ The PrONTO study³³ showed a promising effect, although the SAILOR study did not. Even with additional IVB, our patients did not show at the final visit the VA improvement that they had gained at three months. Delayed treatment to the recurred exudative change may cause the damage of the photoreceptor cells, resulting in the poor visual outcome. It is possible that more frequent IVB injections might result in more promising final VA. In addition, while our patients were scheduled to visit our clinic for an examination at a 1-2 month interval, monthly examinations would be essential to improve visual prognosis.

In the current study, IVB did result in a regression of type 2 CNV secondary to PCV. In 36% of eyes, however, the polypoidal lesions did not disappear with IVB, and it did not diminish at all the branching vascular network. The reason why IVB is

less effective against the PCV lesion itself is uncertain. One possible explanation is the location of the vascular lesion of PCV, which is situated beneath the retinal pigment epithelium.⁸ Another reason may be that VEGF is more weakly involved in vascular components of PCV than it is in CNV secondary to AMD. Based on the visual prognosis of eyes with PCV that received other treatments (i.e., laser photocoagulation or PDT), the recurrence of the vascular lesion may be the most crucial for the long-term treatment effect on PCV.^{22, 26-28} In PCV, repeated treatment with IVB may be necessary to avoid recurrence. Furthermore, combination therapy with PDT might be superior to IVB monotherapy in order to reduce recurrences.^{16, 18}

The current study included five eyes with relatively good initial VA (better than 0.5 on a Landolt chart), but as all eyes showed an exudative change with subfoveal or juxtafoveal PCV, visual prognosis may be poor without any treatments. PDT may cause severe hemorrhagic complications in eyes with PCV,³⁴ and, in the clinical setting, it may be difficult to treat with PDT those eyes that have PCV and good VA.

In eyes with PCV, IVB might be safer than is PDT. Previously, Gomi et al.¹⁴ used IVB in eyes with PCV that had good VA and maintained the initial VA for three months. In the current study in which IVB was used, all 5 eyes with good initial VA maintained their VA for 12 months. However, one of these five eyes developed a tear in the retinal pigment epithelium. Eyes with PCV often show a serosanguineous PED,³⁵

and when a large PED is seen beneath the fovea, it should be kept in mind that development of a tear in the retinal pigment epithelium is a possible complication of IVB.³⁶

Limitations of the current study are the various treatment regimens used and the
5 small sample size. However, despite these short-comings, our findings suggest that IVB can maintain VA for at least 12 months in eyes with PCV. In addition, Reche-Frutos et al.²⁹ recently reported the promising short-term effects of ranibizumab for PCV, and anti-VEGF therapy remains an option for the treatment of PCV. Therefore, prospective studies with long-term follow-up are needed to
10 evaluate the safety and efficacy of IVB for the treatment of PCV.

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Figure legend

Figure 1. Mean foveal thickness (A) and mean visual acuity (VA) in logMAR fashion (B) in eyes with polypoidal choroidal vasculopathy treated with intravitreal injections of bevacizumab. * $P < 0.01$, $^{\dagger}P < 0.05$, compared with pretreatment values. Mo = 5 month(s).

Figure 2. Polypoidal choroidal vasculopathy that was treated successfully with intravitreal injections of bevacizumab (patient 2). (A) Funduscopy photograph shows massive subfoveal exudation with surrounding subretinal hemorrhage. Visual acuity of the left eye was 0.15. (B) Horizontal (upper) and vertical (lower) optical coherence tomographic images along white arrows shown in the fundus photograph reveal a sharp protrusion of retinal pigment epithelium with overlying subretinal exudate. (C) Fluorescein angiography reveals classic subfoveal choroidal neovascularization (CNV). (D) Indocyanine green angiography reveals a branching vascular network terminating in two polypoidal lesions (arrow) and type 2 CNV (long arrow). This eye was treated with 3 monthly injections of bevacizumab and 3 additional injections. (E) Twenty-four months after the initial treatment, funduscopy photograph shows fibrosis and surrounding atrophy of retinal pigment epithelium. Visual acuity remained at 0.15. (F) Horizontal (upper) and vertical (lower) optical

coherence tomographic images along white arrows shown in the fundus photograph

reveal minimal exudative change with a protrusion of retinal pigment epithelium. (G)

Fluorescein angiography shows minimal leakage. (H) Indocyanine green

angiography reveals disappearance of both the polypoidal lesions and the type 2 CNV,

5 but the branching vascular network is still visible.

Figure 3. Recurrence of exudative change after successful treatment of the

polypoidal lesion with intravitreal injections of bevacizumab (patient 15). (A)

Funduscopy photograph shows large pigment epithelial detachment with reddish

10 orange nodules. Visual acuity of the left eye was 0.6. (B) Fluorescein angiography

reveals occult choroidal neovascularization (CNV). (C) Indocyanine green

angiography shows a branching vascular network terminating in many polypoidal

lesions. (D) Horizontal (left) and vertical (right) optical coherence tomographic

images along white arrows shown in the fundus photograph reveal a sharp protrusion

15 of the retinal pigment epithelium with overlying subretinal exudates and retinal edema.

This eye was treated with 3 monthly injections of bevacizumab. (E) Four months

after the initial treatment, funduscopy examination shows a decrease in the exudative

change. Visual acuity had improved to 0.8. (F) Fluorescein angiography reveals no

classic CNV. (G) Indocyanine green angiography reveals disappearance of the

polypoidal lesions, but the branching vascular network is still visible. (H) Horizontal

(left) and vertical (right) optical coherence tomographic images along white arrows

indicated in the fundus photograph show substantially reduced exudative change. (I)

Horizontal (left) and vertical (right) optical coherence tomographic images obtained at

5 12 months show a recurrence of the subretinal fluid. Visual acuity at this time was

0.7.

Figure 4. Intravitreal injections of bevacizumab improved visual acuity in spite of no

change in the polypoidal lesions or in the branching vascular network (patient 9). (A)

10 Fluorescein angiography shows classic choroidal neovascularization (CNV). (B)

Indocyanine green angiography reveals a branching vascular network that terminates

in two polypoidal lesions (arrows). (C) Horizontal (left) and vertical (right) optical

coherence tomographic images along white arrows shown in the fluorescein

angiogram reveal a sharp protrusion of the retinal pigment epithelium with an

15 overlying subretinal exudate. Visual acuity of this eye was 0.3, and it was treated

with 4 injections of bevacizumab. (D) Eight months after the initial treatment,

fluorescein angiography shows minimal leakage. (E) Indocyanine green

angiography shows unchanged polypoidal lesions and unchanged branching vascular

network. (F) Horizontal (left) and vertical (right) optical coherence tomographic

images show no exudative change but remaining cystoid spaces. Visual acuity of the eye at this time was 0.5. (G) Horizontal (left) and vertical (right) optical coherence tomographic images obtained at 19 months show no cystoid spaces. Visual acuity was improved to 0.7.

5

Figure 5. Mean foveal thickness (A) and mean visual acuity in logMAR fashion (B) in eyes with polypoidal choroidal vasculopathy treated with intravitreal injections of bevacizumab. All of these eyes had good pretreatment visual acuity (VA) (better than 0.5). * $P < 0.05$, compared with pretreatment values. Mo = month(s).

10

Figure 6. A tear of the retinal pigment epithelium (RPE) seen in polypoidal choroidal vasculopathy after intravitreal injections of bevacizumab (patient 16). (A)

Funduscopy photograph shows a pigment epithelial detachment (PED) with a large reddish orange nodule. Visual acuity of this eye was 1.2. (B) Fluorescein

15

angiography shows hyperfluorescence reflecting the PED. (C) Indocyanine green

angiography reveals a branching vascular network terminating in two polypoidal

lesions (arrows) at the edge of the PED. (D) Horizontal (left) and vertical (right)

optical coherence tomographic images along white arrows in the fundus photograph

show a sharp protrusion of the retinal pigment epithelium due to a polypoidal lesion

(arrow) at the edge of the PED. The eye was treated with 3 monthly injections of

bevacizumab. **(E)** Three months after the initial treatment, funduscopy examination

shows a large tear of the RPE (arrowheads). Visual acuity had decreased to 0.8.

(F) Fluorescein angiography shows a window defect due to a tear of the RPE. **(G)**

5 No polypoidal lesions are seen on indocyanine green angiography. Folded RPE

shows a blockage of the fluorescence (arrow). **(H)** Horizontal (left) and vertical

(right) optical coherence tomographic images along white arrows shown in the fundus

photograph reveal increased choroidal fluorescence due to a lack of RPE

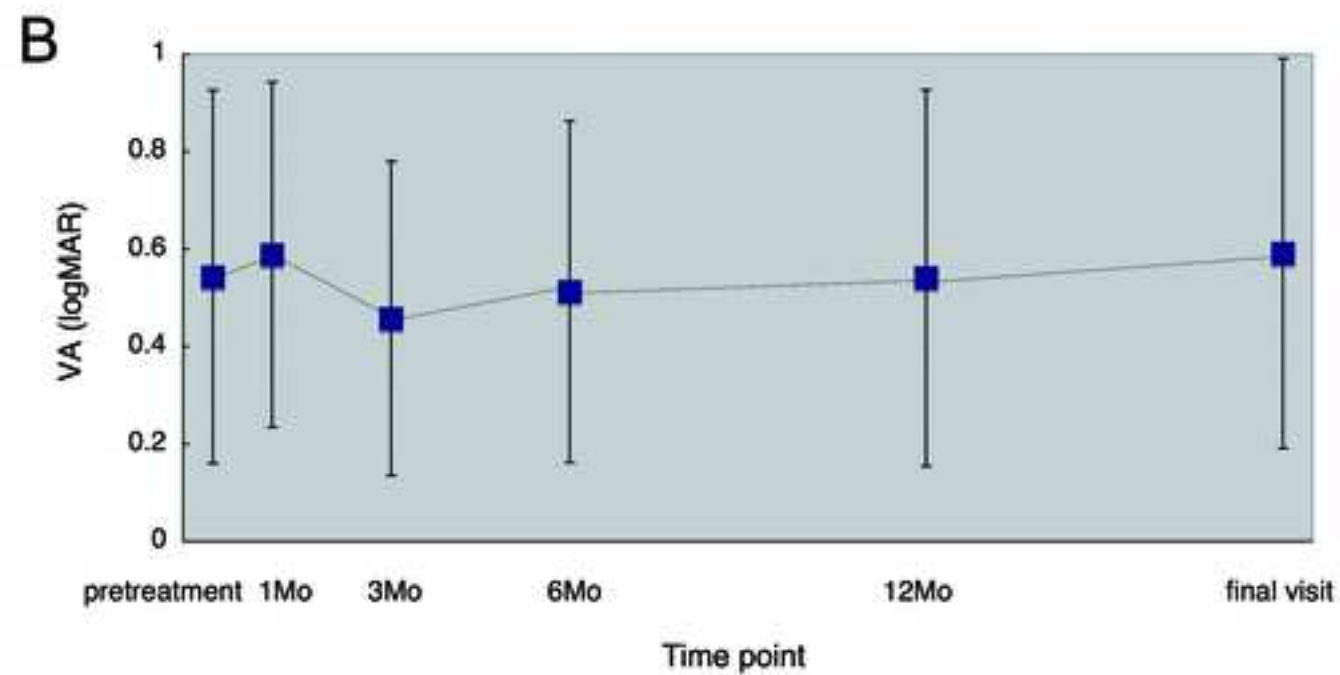
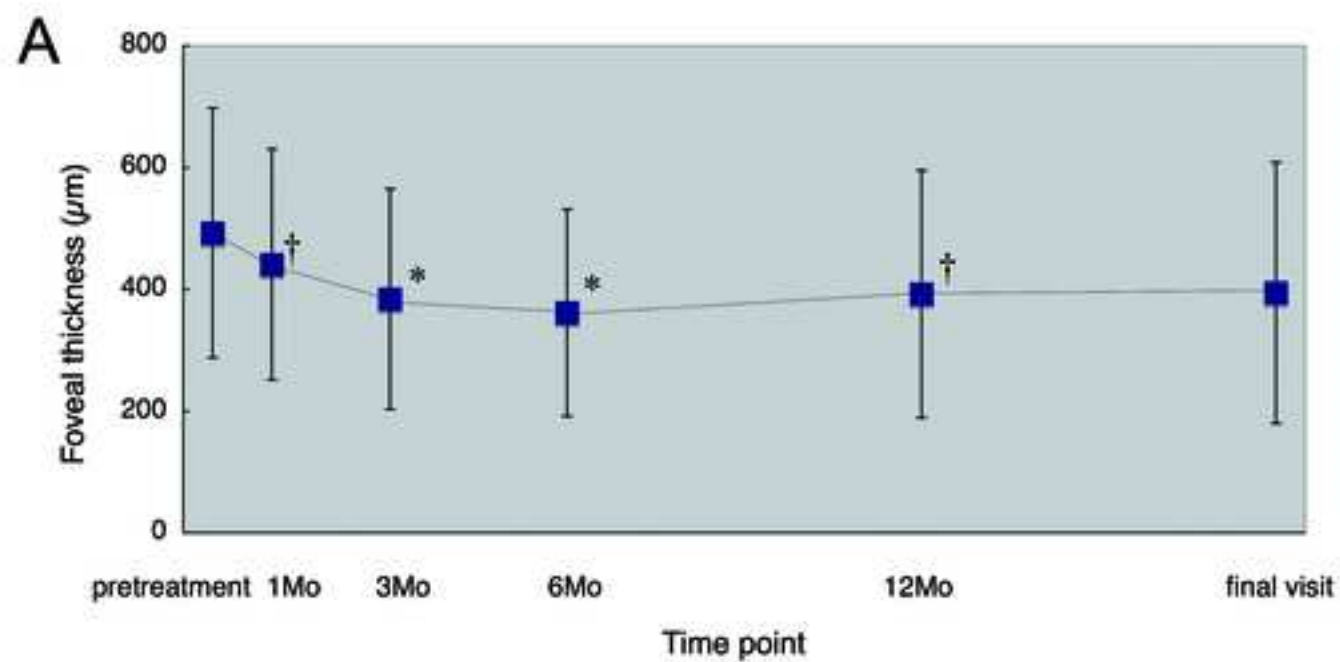
(arrowheads). At 12 months, visual acuity had decreased to 0.4.

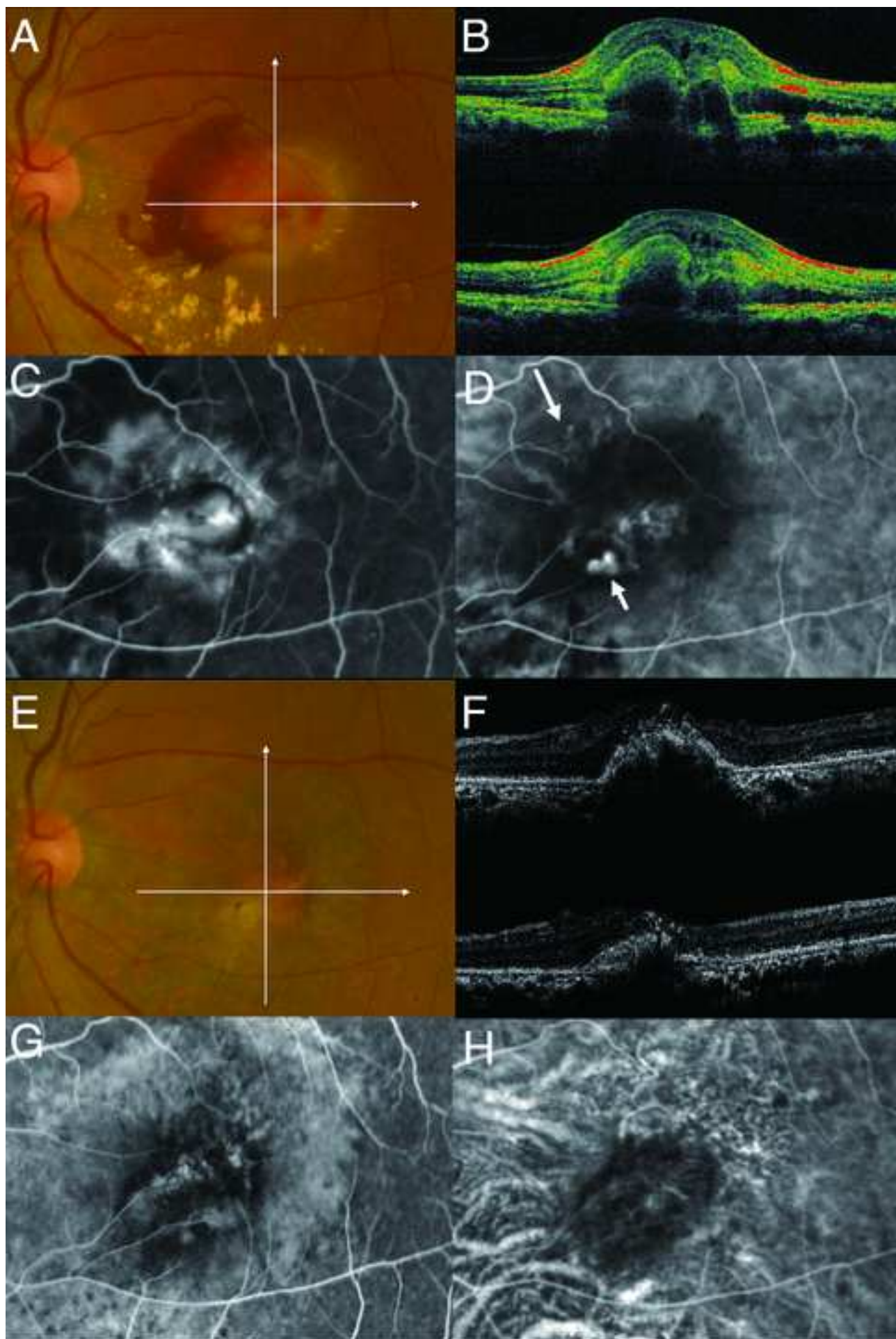
Table 1. Characteristics of eyes with polypoidal choroidal vasculopathy treated with IVB

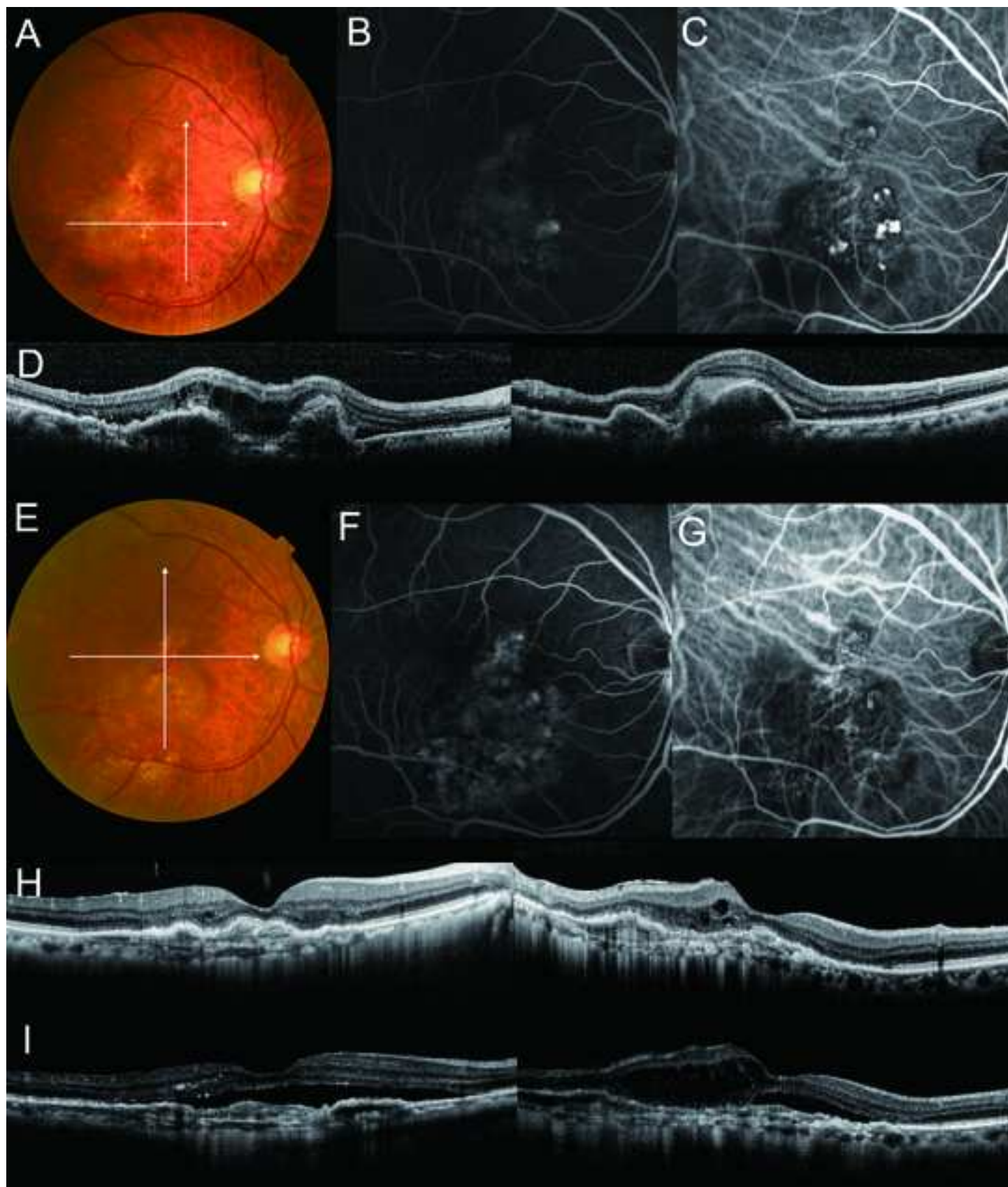
Patient	Pretreatment condition						Total number of IVB	Final condition			Follow-up (Mos)	Complica- tions
	Age / Gender/ RL	Previous treatment	Subfoveal lesion	VA	Foveal thickness (μm)	Initial IVB		VA	Foveal thickness (μm)	Retinal condition		
1	75/M/R	None	BVN	0.3	184	3 monthly injections	4	0.4	140	Dry	30	None
2	68/F/L	None	PL	0.15	850	3 monthly injections	6	0.15	349	Fibrosis	24	None
3	80/M/R	None	BVN	0.1	358	Single injection	5	0.1	763	Exudative	27	None
	80/M/L	None	BVN	0.5	450	Single injection	5	0.2	756	Exudative	23	None
4	74/M/R	PDT	BVN	0.1	415	Single injection	3	0.1	276	Slightly exudative	26	None
5	79/M/L	PDT	BVN	0.09	500	Single injection	2	0.06	204	Fibrosis	26	None
6	78/F/R	None	BVN	0.1	250	Single injection	2	0.2	59	Dry	23	None
7	82/M/R	None	PL	0.5	666	Single injection	3	0.3	280	Dry	22	None
8	80/M/L	None	PL	0.3	363	3 monthly injections	3	0.2	503	Fibrosis	20	None
9	72/M/R	None	BVN	0.3	456	Single injection	6	0.7	232	Dry	19	None
10	75/M/R	None	BVN	0.1	656	Single injection	4	0.06	652	Exudative	16	None
11	85/M/R	PDT x 2	BVN	0.2	969	3 monthly injections	6	0.15	704	Exudative	13	None
12	73/M/R	None	PED	0.7	345	Single injection	1	1.2	286	Dry	26	None
13	60/M/L	None	PL	0.8	633	Single injection	2	0.7	463	Dry	19	None
14	73/M/R	None	BVN	0.6	356	3 monthly injections	6	0.7	322	Slightly exudative	13	None
15	68/M/L	None	BVN	0.8	432	3 monthly injections	6	0.7	381	Dry	13	None
16	76/M/L	None	PED	1.2	484	3 monthly injections	4	0.4	330	Dry	12	RPE tear

IVB, intravitreal injection of bevacizumab; PDT, photodynamic therapy; BVN, branching vascular network; PL, polypoidal lesion; PED, pigment epithelial detachment; RPE, retinal pigment epithelium; Mos, months.

Figure 1
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